conversion of Arg170 to an amino acid selected from the group consisting of histidine, tyrosine, phenylalanine and threonine.

REMARKS

According to the Official Action, Claims 16-20 and 25 were objected to as depending from a non-elected base claim. Claims 16-18, 20 and 25 have been amended to depend from Claim 1. Claim 19 depends from Claim 18. Therefore, each of Claims 16-20 and 25 depends from Claim 1 either directly or indirectly. Accordingly, reconsideration and withdrawal of the objection to Claims 16-20 and 25 is respectfully requested.

The Official Action also required an election of a single disclosed species of modified arrestin for further prosecution on the merits. Applicants hereby elect, with traverse and for purposes of examination only, the modified form of β-arrestin2 wherein Arg170 is converted to Glu (see page 36, lines 2-3 of the specification).

The restriction requirement is respectfully traversed for the following reasons. According to the MPEP, "[w]here only generic claims are presented, no restriction can be required except in those applications where the generic claims recite such a multiplicity of species that an unduly extensive and burdensome search is necessary." See MPEP §809.02(d). According to the Official Action, all of the pending claims that have not been withdrawn from consideration (i.e., Claims 1, 6-13 and 15-25) are generic claims. Further, Applicants have already received an action on the merits for these claims. Therefore, all of these claims have presumably already been searched. In view of the above, it is respectfully submitted that the requirement that the search be "unduly extensive and burdensome" in order for a restriction to be appropriate has not been met. Accordingly, reconsideration and withdrawal of the restriction requirement is respectfully requested.

Also according to the Official Action, the specification allegedly does not comply with 37 C.F.R. § 1.84(U)(1), since Figures 10B, 11B, 12B and 13B are each presented on multiple panels which are not properly numbered. Accordingly, formal drawings containing the appropriate legends for these figures are submitted herewith. Additionally, the "Brief Description of the Drawings" section of the specification has been amended to correspond to the new figure numbering.

Also according to the Official Action, the drawings in the Application allegedly do not comply with 37 C.F.R. §1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims whenever a reference is made to that sequence. Accordingly, reference to the sequence identification numbers of each sequence appearing in the drawings has been made in the "Brief Description of the Drawings". Reconsideration and withdrawal of the objection to the drawings is therefore respectfully requested.

Claims 1, 6-13 and 15-25 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. According to the Official Action, "[a] critical element of the disclosed invention is the requirement that each member of a pair of interacting proteins be fused to one member of a pair of complementary β-galactosidase mutants" (page 4, numbered paragraph 7 of the Official Action). Claims 1, 6-13 and 15-25 were also rejected under 35 U.S.C. §101 because the disclosed invention was allegedly inoperative and lacked utility for the reasons given above. These rejections are respectfully traversed.

Claims 1 and 9 have been amended to recite a cell that expresses a GPCR as a fusion protein to a first mutant form of a reporter enzyme and an arrestin as a fusion protein to a second mutant form of the reporter enzyme complementary to the first mutant form of the reporter enzyme. It is therefore respectfully submitted that independent Claims 1 and 9, as amended, are fully enabled and operative.

It is respectfully submitted that independent Claims 6, 7 and 8 are also fully enabled and operative. Claim 6 recites "[a] DNA molecule comprising a sequence encoding an arrestin as a fusion protein to a mutant form of a reporter enzyme, wherein said arrestin is modified to enhance binding of said arrestin to a GPCR." Claim 7 recites "[a] DNA construct comprising the following operatively linked elements: a promoter; and a DNA molecule comprising a sequence encoding an arrestin as a fusion protein to a mutant form of a reporter enzyme, wherein said arrestin is modified to enhance binding of said arrestin to a GPCR." Claim 8 recites "[a] cell transformed with a DNA construct comprising the following operatively linked elements: a promoter; and a DNA molecule comprising a sequence encoding an arrestin as a fusion protein to a mutant form of a reporter enzyme, wherein said arrestin is modified to enhance binding of said arrestin to a GPCR."

It is respectfully submitted that none of these claims require the presence of the interacting protein partner for the arrestin (i.e., the GPCR as a fusion protein to a complementary mutant form of the reporter enzyme). Moreover, none of these claims require enzymatic activity since they are not directed to an assay for such activity. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claim 16, 17, 24 and 25 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. These claims have been amended to correct the noted minor informalities. Accordingly, reconsideration and withdrawal of the rejections of these claims is respectfully requested.

Claims 1, 6-13 and 15-25 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 6,342,345 ("Blau") in view of U.S. Patent No. 5,891,646 ("Barak"), the Kovoor et al. publication (hereinafter "Kovoor"), the Gurevich et al. '95 publication (hereinafter "Gurevich '95"), and the Gurevich et al. '97 publication (hereinafter "Gurevich '97").

Claim 1 recites "[a] method of assessing the effect of a test condition on G-protein-coupled receptor (GPCR) pathway activity, comprising:

a) *providing a cell that expresses a GPCR as a fusion protein to a first mutant form of a reporter enzyme and an arrestin as a fusion protein to a second mutant form of the reporter enzyme complementary to the first mutant form of the reporter enzyme,*

wherein said arrestin is modified to enhance binding of said arrestin to said GPCR, wherein said enhanced binding between said arrestin and said GPCR increases sensitivity of detection of said effect of said test condition;

b) exposing the cell to a ligand for said GPCR under said test condition; and

c) monitoring activation of said GPCR by complementation of said first and second mutant forms of the reporter enzyme;

wherein increased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates increased GPCR interaction with the modified arrestin compared to that which occurs in the absence of said test condition, and decreased reporter

enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates decreased GPCR interaction with the modified arrestin compared to that which occurs in the absence of said test condition.

According to the MPEP, when applying 35 U.S.C. §103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). MPEP § 2141.

It is respectfully submitted that the Official Action has failed to establish a *prima facie* case of obviousness. First, in order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Further, the teaching or suggestion to make the claimed combination must be found in the prior art and not in the Applicants' disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

It is respectfully submitted that there is no teaching or suggestion in any of the cited references to combine the reference teachings in the manner suggested in the Official Action. In particular, Blau broadly discloses methods and compositions for detecting protein-protein

interactions using fusion proteins of β-galactosidase mutants. However, Blau fails to disclose the claimed method comprising providing *a cell that expresses a GPCR as a fusion protein to a first mutant form of a reporter enzyme and a modified arrestin as a fusion protein to a second mutant form of the reporter enzyme complementary to the first mutant form of the reporter enzyme.* Further, while Barak teaches an assay method for GPCRs, the assay method of Barak does not involve the complementation of mutant forms of reporter enzyme. In particular, neither the GPCR nor the arrestin molecule in Barak are expressed as a fusion protein to a mutant form of a reporter enzyme. Thus, Barak also fails to disclose the claimed method comprising providing *a cell that expresses a GPCR as a fusion protein to a first mutant form of a reporter enzyme and a modified arrestin as a fusion protein to a second mutant form of the reporter enzyme complementary to the first mutant form of the reporter enzyme.* Kovoor, Gurevich '95, and Gurevich '97 also fail to teach or reasonably suggest the claimed invention. Each of these references discloses various modified forms of arrestin. However, there is no disclosure in any of these references of a method as claimed comprising providing *a cell that expresses a GPCR as a fusion protein to a first mutant form of a reporter enzyme and a modified arrestin as a fusion protein to a second mutant form of the reporter enzyme complementary to the first mutant form of the reporter enzyme.*

Thus, the Official Action has pointed to no specific teaching or suggestion in any of the cited references to combine the reference teachings in the manner suggested. Rather, in order to arrive at the Applicants' invention from the teachings of the cited references, the Official Action makes the following assertions:

> An artisan of ordinary skill in the art of molecular biology would have recognized that the method of Barak, et al. was limited by the fact that it did not allow detection of the direct interaction of the fluorescent labeled β-arrestin employed therein with a specific G protein-coupled receptor. (page 7 of the Official Action)

> That artisan would have realized that the fluorescent labeled β-arrestin would have accumulated at the cell membrane in response to the activation of any G protein-coupled receptor which might be present in the cell. (page 7 of the Official Action)
>
> . . . that artisan would have appreciated the fact that an accurate measurement of the ligand activation of a particular receptor by employing the method of Barak, et al. would require the inclusion of a control consisting of a cell which is otherwise identical to the test cell except for the absence of the receptor of interest. (page 7 of the Official Action)
>
> That artisan would have understood that the method of detecting protein-protein interaction that was described by Blau, et al. would not have required such a control because it measured the direct interaction of two specific proteins and, therefore, would allow one to measure the direct interaction of β-arrestin with a specific G protein-coupled receptor in an intact cell irrespective of the interaction of β-arrestin with any other G protein-coupled receptor which might be present in that cell. (page 7 of the Official Action)
>
> Therefore, that artisan would have found it *prima facie* obvious to have employed the β-galactosidase complementation system of Blau, et al. to detect the interaction of β-arrestin with a particular G protein-coupled receptor to identify agonists and antagonists thereto as taught by Barak, et al. because that artisan would have been more confident that the results obtained by the method of Blau, et al. were representative of the action of the particular receptor of interest. (pages 7-8 of the Official Action)

It is respectfully submitted that the above line of reasoning could only have been arrived at with the benefit of the Applicants' disclosure. For example, the Official Action makes reference to what one of ordinary skill in the art would have "recognized", "realized", "appreciated", "understood" or "found" without providing support for these statements. In fact, it is respectfully submitted that the alleged shortcomings of the Barak assay method referred to in the Official Action are only apparent given the Applicants' disclosure of an improved receptor function assay for G-protein coupled receptors. As set forth in The MPEP:

> . . . the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of Applicants' disclosure must be put aside in reaching this determination . . . The tendency to

> resort to "hindsight" based upon Applicants' disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. MPEP § 2142.

Since the rejection is an impermissible hindsight reconstruction of the Applicants' invention, reconsideration and withdrawal of the rejection is respectfully requested.

Further, the Official Action has also failed to establish that one of ordinary skill in the art could have made the proposed combination or modification with a reasonable expectation of success. It is well established that references can be modified or combined to reject claims as *prima facie* obvious only if there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, at least some degree of predictability is required to show reasonable expectation of success. See MPEP §2143.02. Additionally, the reasonable expectation of success must be found in the prior art and not in the Applicants' disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143.

The Official Action has pointed to no teaching or suggestion in the cited references that would establish that the proposed combination could have been made with a reasonable expectation of success. In fact, it is respectfully submitted that such evidence is not present in any of the cited references. As set forth above, none of the cited references disclose the claimed method comprising providing *a cell that expresses a GPCR as a fusion protein to a first mutant form of a reporter enzyme and a modified arrestin as a fusion protein to a second mutant form of the reporter enzyme complementary to the first mutant form of the reporter enzyme*. In particular, while Blau broadly discloses methods and compositions for detecting protein-protein interactions using fusion proteins of β-galactosidase mutants, Blau does not disclose a method as set forth in Claim 1 wherein complementation of 1) a fusion protein of a GPCR and a first mutant form of a reporter enzyme and 2) a fusion protein of a modified arrestin and a second mutant form of the

reporter enzyme complementary to the first mutant form of the reporter enzyme is monitored. In addition, while Barak teaches an assay method for GPCRs, the assay method of Barak does not involve the complementation of mutant forms of reporter enzyme as set forth in Claim 1. In particular, neither the GPCR nor the β-arrestin molecule in Barak are expressed as a fusion protein to a mutant form of reporter enzyme. Kovoor, Gurevich '95, and Gurevich '97, which disclose various modified forms of arrestin, also fail to teach or reasonably suggest the method as set forth in Claim 1. Moreover, none of these references teach or reasonably suggest the use of modified forms of arrestin as set forth in Claim 1. Since none of the cited references adequately establishes that the complementation of mutant forms of reporter enzyme can be adapted for use with G-protein coupled receptors with a reasonable expectation of success, it is respectfully submitted that the claims are patentable over the cited references. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Additionally, the modification of the Barak reference in the manner set forth in the Official Action would fail to establish a case of *prima facie* obviousness since the modification would involve a change in the principle of operation of the reference. It is well established that if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). In Ratti, the court reversed an obviousness rejection holding that the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.). See MPEP §2143.01. Similarly, the modification proposed in the Official Action would require a substantial reconstruction and redesign of the assay method of Barak. Namely, in the assay methods of

Barak, the test cell expresses GPCR and a conjugate of β-Arrestin and a visually detectable molecule. According to Barak, the test cell is then observed for evidence of translocation of the detectable molecule (see, for example, column 2, lines 35-37 of Barak). For example, the translocation of the visually detectable molecule (e.g., from the cytosol to the cell edge) can be used to assay G-protein coupled receptor activity (see, for example, column 2, lines 43-52 of Barak). Thus, in Barak the movement of a visually detectable molecule bound to the β-arrestin molecule is being monitored. The principle of operation of Barak is therefore radically different than that set forth in Claim 1 wherein *the complementation of mutant forms of a reporter enzyme*, one expressed as a fusion protein to a GPCR and another as a fusion protein to an interacting protein partner, is being monitored. Accordingly, it is respectfully submitted that the invention as set forth in Claim 1 is patentable over the cited references. In view of the above, reconsideration and withdrawal of the rejection of Claim 1 is therefore respectfully requested.

Claims 15-20 and 25 depend either directly or indirectly from Claim 1 and are therefore also patentable over the cited references for at least the reasons set forth above with respect to Claim 1. Reconsideration and withdrawal of the rejections of these claims is therefore also respectfully requested.

Claim 9 recites "[a] method of assessing the effect of a test condition on G-protein-coupled receptor (GPCR) pathway activity, comprising:

a) *providing a cell that expresses a GPCR as a fusion protein to a first mutant form of a reporter enzyme and an arrestin as a fusion protein to a second mutant form of the reporter enzyme complementary to the first mutant form of the reporter enzyme,*

wherein said arrestin is modified by introducing a point mutation in a phosphorylation-recognition domain to remove a requirement for phosphorylation of said GPCR for arrestin

binding to permit binding of said arrestin to said GPCR in said cell regardless of whether said GPCR is phosphorylated,

b) exposing the cell to a ligand for said GPCR under said test condition; and

c) monitoring activation of said GPCR by complementation of said first and second mutant forms of the reporter enzyme;

wherein increased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates increased GPCR interaction with the modified arrestin compared to that which occurs in the absence of said test condition, and decreased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates decreased GPCR interaction with the modified arrestin compared to that which occurs in the absence of said test condition.

Claim 9 is therefore patentable over the cited references for at least the reasons set forth above for Claim 1. Additionally, Claims 10-13 and 21-24 depend either directly or indirectly from Claim 9 and are therefore also patentable over the cited references. Reconsideration and withdrawal of the rejections of these claims is therefore also respectfully requested.

Claim 6 recites "[a] DNA molecule comprising a sequence encoding an arrestin as a fusion protein to a mutant form of a reporter enzyme, wherein said arrestin is modified to enhance binding of said arrestin to a GPCR."

Claim 7 recites "[a] DNA construct comprising the following operatively linked elements:

a promoter; and

a DNA molecule comprising a sequence encoding an arrestin as a fusion protein to a mutant form of a reporter enzyme, wherein said arrestin is modified to enhance binding of said arrestin to a GPCR."

Claim 8 recites "[a] cell transformed with a DNA construct comprising the following operatively linked elements:

a promoter; and

a DNA molecule comprising a sequence encoding an arrestin as a fusion protein to a mutant form of a reporter enzyme, wherein said arrestin is modified to enhance binding of said arrestin to a GPCR."

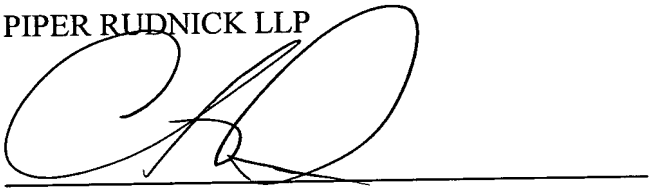
Each of Claims 6, 7 and 8 therefore recites a DNA molecule comprising a sequence encoding *an arrestin as a fusion protein to a mutant form of a reporter enzyme*. It is respectfully submitted that none of the cited references teach or reasonably suggest the claimed invention. In particular, while Blau teaches the detection of molecular interactions by using fusion proteins of enzyme mutants generally, Blau fails to disclose assays for arrestin. Further, while Barak discloses assays for GPCRs involving arrestin, neither the GPCR nor the arrestin are expressed as a fusion protein to a mutant form of reporter enzyme. Kovoor, Gurevich '95, and Gurevich '97 also fail to teach or reasonably suggest the claimed invention. These references merely disclose various modified forms of arrestin. Accordingly, it is respectfully submitted that none of the cited references teach or reasonably suggest the invention as set forth in Claims 6, 7 and 8. Reconsideration and withdrawal of the rejections of these claims is therefore respectfully requested.

CONCLUSION

All rejections having been addressed by the present amendments and response, Applicants believe that the present case is in condition for allowance and respectfully request early notice to that effect. If any issues remain to be addressed in this matter which might be resolved by discussion, the Examiner is respectfully requested to call Applicants' undersigned counsel at the number indicated below.

Respectfully submitted,

PIPER RUDNICK LLP



Steven B. Kelber
Registration No. 30,073
Attorney of Record

Christopher W. Raimund
Registration No. 47,258

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No. (202) 861-3900
Facsimile No. (202) 223-2085

MARKED-UP COPY OF PARAGRAPHS, AS AMENDED

Replacement for second full paragraph at page 20, lines 9-15:

[FIGURE 10A. pICAST ALC: Vector for expression of β-galΔα as a C-terminal fusion to the target protein. This construct contains the following features: MCS, multiple cloning site for cloning the target protein in frame with the β-galΔα; GS Linker, (GGGGS)n; NeoR, neomycin resistance gene; IRES, internal ribosome entry site; ColElori, origin of replication for growth in E. coli; 5'MoMuLV LTR and 3'MoMuLV LTR, viral promoter and polyadenylation signals from the Moloney Murine leukemia virus.]

FIGURES 10B-10P. Nucleotide sequence for pICAST ALC (SEQ ID NO: 01).

Replacement for fourth full paragraph at page 20, line 18 through page 21, line 2:

[FIGURE 11A. pICAST ALN: Vector for expression of β-galΔα as an N-terminal fusion to the target protein. This construct contains the following features: MCS, multiple cloning site for cloning the target protein in frame with the β-galΔα; GS Linker, (GGGGS)n; NeoR, neomycin resistance gene; IRES, internal ribosome entry site; ColElori, origin of replication for growth in E. coli;

5'MoMuLV LTR and 3'MoMULV LTR, viral promoter and polyadenylation signals from the Moloney Murine leukemia virus.]

FIGURES 11B-11L. Nucleotide sequence for pICAST ALN (SEQ ID NO: 02).

Replacement for first full paragraph at page 21, line 3, and insert therefor the following:

[FIGURE 11B. Nucleotide sequence for pICAST ALN.]

FIGURES 11B-11L. Nucleotide sequence for pICAST ALN (SEQ ID NO: 02).

Delete the third full paragraph at page 21, line 11, and insert therefor the following:

[FIGURE 12B. Nucleotide sequence for pICAST OMC.]

FIGURES 12B-12L. Nucleotide sequence for pICAST OMC (SEQ ID NO: 03).

Replacement for fifth full paragraph at page 21, line 11, and insert therefor the following:

[FIGURE 13B. Nucleotide sequence for pICAST OMN.]

FIGURES 13B-13L. Nucleotide sequence for pICAST OMN (SEQ ID NO: 04).

SERIAL NO. 09/759,152

DOCKET NO.: 4085-235-27 CIP

MARKED-UP COPY OF AMENDED CLAIMS

1. (Amended) A method of assessing the effect of a test condition on G-protein-coupled receptor (GPCR) pathway activity, comprising:

a) providing a cell that expresses a GPCR as a fusion protein to [one] a first mutant form of a reporter enzyme and an [interacting protein partner] arrestin as a fusion protein to [another] a second mutant form of the reporter enzyme complementary to the first mutant form of the reporter enzyme,

[wherein said cell also expresses an arrestin,] wherein said arrestin is modified to enhance binding of said arrestin to said GPCR, wherein said enhanced binding between said arrestin and said GPCR increases sensitivity of detection of said effect of said test condition;

b) exposing the cell to a ligand for said GPCR under said test condition; and

c) monitoring activation of said GPCR by complementation of said first and second mutant forms of the reporter enzyme;

wherein increased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates increased GPCR interaction with [its interacting protein partner] the modified arrestin compared to that which occurs in the absence of said test condition, and decreased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates decreased GPCR interaction with [its interacting protein partner] the modified arrestin compared to that which occurs in the absence of said test condition.

6. (Amended) A DNA molecule comprising a sequence encoding [a biologically active hybrid arrestin, wherein said hybrid arrestin comprises] an arrestin as a fusion protein to [one] a

mutant form of a reporter enzyme, [and] wherein said [hybrid] arrestin is modified to enhance binding of said arrestin to a GPCR.

7. (Amended) A DNA construct [capable of directing the expression of a biologically active hybrid an arrestin in a cell,] comprising the following operatively linked elements:

a promoter; and

a DNA molecule comprising a sequence encoding [a biologically active hybrid arrestin, wherein said hybrid arrestin comprises] an arrestin as a fusion protein to [one] a mutant form of a reporter enzyme, [and] wherein said [hybrid] arrestin is modified to enhance binding of said arrestin to a GPCR.

8. (Amended) A cell transformed with a DNA construct [capable of expressing a biologically active hybrid arrestin in a cell,] comprising the following operatively linked elements:

a promoter; and

a DNA molecule comprising a sequence encoding [a biologically active hybrid arrestin, wherein said hybrid arrestin comprises] an arrestin as a fusion protein to [one] a mutant form of a reporter enzyme, [and] wherein said [hybrid] arrestin is modified to enhance binding of said arrestin to a GPCR.

9. (Amended) A method of assessing the effect of a test condition on G-protein-coupled receptor (GPCR) pathway activity, comprising:

a) providing a cell that expresses a GPCR as a fusion protein to [one] a first mutant form of a reporter enzyme and an [interacting protein partner] arrestin as a fusion protein to [another] a second mutant form of the reporter enzyme complementary to the first mutant form of the reporter enzyme,

[wherein said cell also expresses an arrestin,] wherein said arrestin is modified by

introducing a point mutation in a phosphorylation-recognition domain to remove a requirement for phosphorylation of said GPCR for arrestin binding to permit binding of said arrestin to said GPCR in said cell regardless of whether said GPCR is phosphorylated,

b) exposing the cell to a ligand for said GPCR under said test condition; and

c) monitoring activation of said GPCR by complementation of said first and second mutant forms of the reporter enzyme;

wherein increased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates increased GPCR interaction with [its interacting protein partner] the modified arrestin compared to that which occurs in the absence of said test condition, and decreased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates decreased GPCR interaction with [its interacting protein partner] the modified arrestin compared to that which occurs in the absence of said test condition.

16. (Amended) The method of Claim [14] 1, wherein said modified arrestin comprises conversion of Arg169 to an amino acid selected from the group consisting of histidine, tyrosine, phenylalanine and threonine.

17. (Amended) The method of Claim [14] 1, wherein said modified arrestin comprises conversion of Val170 to alanine.

18. (Amended) The method of Claim [14] 1, wherein said arrestin is selected from the group consisting of β-arrestin1 and β-arrestin2, and wherein said β-arrestin1or said β-arrestin2 is truncated for all or part of a carboxyl-terminal half of said β-arrestin1 or said β-arrestin2.

20. (Amended) The method of Claim [14] 1, wherein said arrestin is a chimera of β-arrestin1, β-arrestin2 and/or visual arrestin.

24. (Amended) The method of Claim 10, wherein said arrestin is [β-arrestin1] β-arrestin2 and wherein said β-arrestin2 is mutated to convert Arg170 to an oppositely charged residue.

25. (Amended) The method of Claim [14] 1 , wherein said modified arrestin comprises conversion of Arg170 to an amino acid selected from the group consisting of histidine, tyrosine, phenylalanine and threonine.